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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 08/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/074,978	GUO ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-10,12-14,30,33 and 78-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-10,12-14,30,33 and 78-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/18/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 5-10, 12-14, 30, 33, and 78-84 are pending in the application.

[2] Applicant's amendment to the claims, filed April 26, 2004, is acknowledged.

[3] Receipt of a petition under 37 CFR 1.48(b) to change inventorship, filed April 26, 2004, is acknowledged.

Election/Restriction

[4] Applicant's election without traverse of Group II, original claims 5-14, 30, and 33, drawn to an isolated nucleic acid encoding SEQ ID NO:24 including SEQ ID NO:23, a vector, a cell, a pharmaceutical composition, and a kit.

Correction of Inventorship

[5] In view of the papers filed April 26, 2004, the inventorship in this nonprovisional application has been changed by the deletion of Ballinger, Robert A., Blalock, Angela D., Boldog, Ferenc L., Casman, Stacie J., Fernandes, Elma, Guo, Xiaojia Sasha, Gusev, Vladimir Y., Hermann, John, Heyes, Melvyn P., Ioime, Noelle, Ji, Weizhen, Kekuda, Ramesh, Leite, Mario W., Liu, Yi, Mezes, Peter D., Patturajan, Meera, Pena, Carol E.A., Rastelli, Luca, Shenoy, Suresh G., Shimkets, Richard A., Spytek, Kimberly A., Taupier, Raymond J., Tchernev, Velizar T., and Vemet, Corine.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of the file jacket and PTO PALM data to reflect the inventorship as corrected.

Information Disclosure Statement

[6] All references cited on the information disclosure statement (IDS) filed September 18, 2002, with the exception of references C389, C390, and C391, have been considered by the examiner. References C389-C391 have not been considered as no date of public availability is listed on the IDS as required by 37 CFR 1.98. A copy of the IDS is attached to the instant Office action.

Oath/Declaration

[7] The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because: It was not executed in accordance with either 37 CFR 1.66 or 1.68. The examiner can find no signature/date for inventor Yi Liu.

Specification/Informalities

[8] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is

suggested: -- Nucleic Acid Encoding a Polypeptide Homologous to a Potassium Channel Protein --.

[9] The attempt to incorporate subject matter into this application by reference to a hyperlink embedded in the specification at, for example, page 16, line 8, and all other instances in the specification is improper. Incorporation of subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP 608.01 regarding hyperlinks in the specification and 608.01(p), paragraph I regarding incorporation by reference. It is noted that the instant specification is 549 pages in length. Applicants' cooperation in identifying other hyperlinks in the specification and making the appropriate correction(s) is appreciated.

[10] The use of the trademarks "Triton®" and "Thesit®" has been noted in this application. These and all other trademarks used in the specification should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. It is noted that the instant specification is 549 pages in length. Applicants' cooperation in identifying other trademarks in the specification and making the appropriate correction(s) is appreciated.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

[11] Claims 5-10, 12-14, 30, 33, and 78-84 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or well-established utility. Claims 5-10, 12-14, and 78-84 are drawn to an isolated polynucleotide encoding SEQ ID NO:24 including SEQ ID NO:23, variants thereof, and complements thereof. Claims 12-14 are drawn to a vector and cell comprising the claimed nucleic acid. Claims 30 and 33 are drawn to a pharmaceutical composition comprising the claimed nucleic acid and a kit comprising said pharmaceutical composition.

The specification discloses that SEQ ID NO:23 encodes the "mature" open reading frame of SEQ ID NO:24 (p. 66). The specification asserts that SEQ ID NO:24 (also referred to as NOVX8) shares a high level of sequence identity to potassium channel proteins, particularly an acid-sensitive potassium channel protein referred to as TASK (pp. 66-67). The specification asserts that, based on the sequence similarity between acid-sensitive potassium channel protein TASK and SEQ ID NO:24, SEQ ID NO:23 encodes a TASK-like protein. However, it should be noted that there is no indication in the specification as to how SEQ ID NO:24 is "like" a TASK protein. For example, is SEQ ID NO:24 "like" a TASK protein only at the level of amino acid identity or is SEQ ID NO:24 further "like" a TASK protein by having the same function as TASK? Further, it is noted that the SEQ ID NO:24, while sharing a high level of sequence

identity to potassium channel proteins, is not completely identical to any potassium channel protein and there is no disclosure that SEQ ID NO:24 exhibits the amino acids necessary for biological function of potassium channel proteins. Absent an assertion that SEQ ID NO:24 has potassium channel protein biological activity and evidence that SEQ ID NO:24 has exhibits such activity, it is unclear as to whether SEQ ID NO:24 has potassium channel protein biological activity. Even assuming *arguendo* the specification asserted SEQ ID NO:24 has potassium channel protein biological activity and provided evidence in support thereof, the examiner knows of no well-established utility for a potassium channel protein. Further, even if SEQ ID NO:24 has potassium channel protein biological activity, it is noted that there is no indication that the claimed nucleic acid variants having specifically recited mutations (claims 78-80 and 82-84) also have potassium channel protein biological activity. The specification asserts "[t]he protein similarity information, expression pattern, cellular localization, and map location for the protein and nucleic acid disclosed herein suggest that this... ...Task-like protein may have important structural and/or physiological functions characteristic of the Ion Channel family" (p. 71) and "[t]herefore, the nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications and as a research tool" (p. 71). However, these asserted utilities are not substantial as the specification fails to provide the guidance necessary for use of the claimed nucleic acid for diagnostic and therapeutic applications and as a research tool. Consequently, the asserted utilities are not substantial as further experimentation is required to establish a real-world use for the claimed nucleic acid. See Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (Sup.

Ct. 1966). The specification must teach a skilled artisan how to use what is claimed and not merely provide a blueprint for further experimentation in order for an artisan to identify a use for the claimed invention. As stated in Brenner v. Manson, 383 U.S. 519 535-536, 148 USPQ 689, 696 (1966), "[a] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion". Further, the examiner knows of no well-established utility for the claimed nucleic acid. As such, the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

[12] Claims 5-10, 12-14, 30, 33, and 78-84 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[13] Claims 7, 10, 78-80, and 82-84 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claims 7 and 78-80 are confusing as it is unclear as to how a nucleic acid that encodes SEQ ID NO:24 can simultaneously encode a variant of SEQ ID NO:24. Claim 7 is drawn to a nucleic acid encoding a "naturally-occurring polypeptide variant" of SEQ ID NO:24. Claims 78-80 are drawn to nucleic acids having nucleotide substitutions that, according to page 67, Table 8C, alter the corresponding amino acid. It is suggested that applicants clarify the meaning of the claims.

[b] Claim 10 is indefinite in the recitation of "stringent conditions" as the specification does not define what conditions constitute "stringent". What hybridization conditions are considered "stringent" varies widely in the art depending on the individual situation as well as the person making the determination. As such it is unclear as to the nucleic acid sequences that encode SEQ ID NO:24 that are to be included within the scope of the claim.

[c] Claim 10 is indefinite in the recitation of "complement." The specification defines a nucleic acid that is "complementary" as "[a] nucleic acid molecule that is complementary to the nucleotide sequence shown [in SEQ ID NO:23] is one that is sufficiently complementary to the nucleotide sequence shown [in SEQ ID NO:23] that it can hydrogen bond with little or no mismatches to the nucleotide sequence shown [in SEQ ID NO:23] thereby forming a stable duplex" (p. 291, lines 14-24). In view of this definition, it is unclear as to whether the complement is a full or partial complement and whether the complement is an exact complement or has mismatches with its corresponding complementary strand. It is suggested that applicants clarify the meaning of the term "complement."

[d] Claims 78-80 and 82-84 are indefinite as claim 5 (from which claims 78-80 depend) and claim 81 (from which claims 82-84 depend) recite open claim language, i.e., "comprising," it is unclear as to whether the recited positions are meant to be limited to those nucleotide/amino acid positions of SEQ ID NO:23/24, respectively, or if the recited positions are of any nucleic acid or encoded polypeptide *comprising* SEQ ID NO:23 or SEQ ID NO:24, respectively. For example, position 225 of a nucleic acid comprising SEQ ID NO:23 with an additional 50 nucleotides at the 5'-end of the sequence would not correspond to position 225 of SEQ ID NO:23. In the interest of advancing prosecution, the claims have been interpreted as meaning the recited positions of SEQ ID NO:23/24. It is suggested that applicants clarify the meaning of the claims.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[14] Claims 78-80 and 82-84 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 78-80 are drawn to the nucleic acid of claim 5, having adenine or guanine at position 225, guanine or adenine at position 605, or thymine or cytosine at position 615. Claims 82-84 are drawn to the nucleic acid encoding the polypeptide of claim 81, having glutamine or glycine at position 75, alanine or threonine at position 202, or leucine or proline at position 205.

First, it is noted that the specification and claims as originally filed only provide support for the recited nucleotide positions of SEQ ID NO:23 (not a nucleic acid comprising SEQ ID NO:23) or a nucleic acid encoding a polypeptide having the amino acids SEQ ID NO:24 (not a nucleic acid encoding a polypeptide comprising SEQ ID NO:24). In view of the comprising language, the recited nucleotide or encoded amino acid positions may not correspond to the same positions within SEQ ID NO:23/24. For example, position 225 of a nucleic acid comprising SEQ ID NO:23 with an additional 50 nucleotides at the 5'-end of the sequence would not correspond to position 225 of SEQ ID NO:23. Second, it should be noted that the specification and claims as originally filed fail to provide support for glutamine at position 75 as recited in claim 82.

[15] Claims 6-7, 10, and 81-84 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 6 is drawn to an isolated nucleic acid encoding SEQ ID NO:24, wherein the nucleic acid is a naturally-occurring allelic variant. Claim 7 is drawn to a nucleic acid

encoding a polypeptide comprising SEQ ID NO:24, wherein the nucleic acid encodes a naturally occurring polypeptide variant. Claim 10 is drawn to an isolated nucleic acid that an isolated nucleic acid that hybridizes to SEQ ID NO:23 or a complement thereof. Claims 81-84 are drawn to an isolated nucleic acid encoding an amino acid sequence that differs from SEQ ID NO:24 by a single amino acid.

Regarding all claims, for claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single representative species of the genus of claimed polynucleotides, i.e., SEQ ID NO:23. The specification fails to describe any additional representative species of the claimed genus. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely

variant species cannot be achieved by disclosing only one species within the genus". In the instant case, the claimed genus of polynucleotides encompasses species that are widely variant in both structure and function, including (but not limited to) genomic sequences, allelic variants, and nucleic acid variants encoding polypeptides having function other than the activity of SEQ ID NO:24, e.g., non-functional polypeptides. As such, the disclosure of the single representative species of SEQ ID NO:23 is insufficient to be representative of the attributes and features of *all* species encompassed by the claimed genus of polynucleotides.

Specifically regarding claims 6-7, the Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (Fed. Cir. 1997), quoting *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). Also, MPEP § 2163 states (citing *Amgen*, 927 F.2d at 1206, 18 USPQ2d at 1021), "A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials." In the instant case, the specification discloses a nucleic acid encompassed by the genus. Those sequences that are "naturally-occurring" or encode polypeptides that are "naturally-occurring" are a subset of this genus of nucleic acids. In this case, the specification fails to define those structural features of SEQ ID NO:23 or SEQ ID NO:24

that are commonly possessed by members of the genus such that one can distinguish those nucleic acids that are "naturally-occurring" or encode polypeptides that are "naturally-occurring" from non-naturally occurring nucleic acids. Thus, one skilled in the art cannot visualize or recognize the identity of the members of the genus. As such, the disclosed single representative species does not adequately describe this subset according to its structure so that one of skill in the art can visualize and distinguish those nucleotides or encoded amino acids that are "naturally-occurring," particularly in view of the larger genus that includes both "naturally-occurring" and non-naturally occurring nucleic acids. Therefore, the instant claims are not adequately described.

[16] Even if applicant demonstrates the polynucleotide encoding SEQ ID NO:24 has a specific and substantial or well-established utility, the following rejection still applies. Claims 7, 10, 30, 33, 81, and 83-84 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid encoding SEQ ID NO:24 and a composition comprising a nucleic acid encoding SEQ ID NO:24, does not reasonably provide enablement for the broad scope of claimed variant polynucleotides (claims 6-7, 10, 81, and 83-84) and pharmaceutical compositions (claims 30 and 33). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are

summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: Regarding claims 7, 10, 81, and 83-84, the claims are so broad as to encompass a vast number of variants of SEQ ID NO:23 or a nucleic acid encoding SEQ ID NO:24. The broad scope of claimed polynucleotides is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides broadly encompassed by the claims. In this case the disclosure is limited to a polynucleotide encoding SEQ ID NO:24 and a composition comprising a nucleic acid encoding SEQ ID NO:24. Regarding the interpretation of claims 81 and 83-84, it is noted that if alanine is at position 202 or if leucine is at position 205, then the single amino acid substitution must be at some other unidentified amino acid as these residues are present in SEQ ID NO:24. Claim 82, on the other hand, does not recite an amino acid that is present in SEQ ID NO:24 and the variant must be either Gln or Gly at position 75. Thus, it would not constitute undue experimentation to make the scope of claimed nucleic acids.

- The lack of guidance and working examples: Regarding claims 7, 10, 81, and 83-84, the specification provides only a single working example of the claimed polynucleotide, i.e., SEQ ID NO:23. This single working example fails to provide the necessary guidance for making and/or using the entire scope of claimed polynucleotides. The specification fails to provide guidance regarding those nucleotides of SEQ ID NO:23 or amino acids of SEQ ID NO:24 that may be altered by substitution, insertion, and deletion with an expectation of maintaining the desired activity. Furthermore, the specification fails to provide guidance as to how to use those variant nucleic acids that encode polypeptides having activities other than the desired activity, e.g., nucleic acids encoding non-functional polypeptides. Regarding claims 30 and 33, it is noted that the term "pharmaceutical composition" implies a therapeutic use. However, the specification fails to provide even a single working example of the claimed nucleic acid being used for a therapeutic utility and the specification fails to provide the specific guidance, e.g., the specific disease to be targeted, specific dosage, specific route(s) of administration, that is necessary for a therapeutic use of the claimed nucleic acid.

- The high degree of unpredictability in the art: Regarding claims 7, 10, 81, and 83-84, the nucleotide sequence of an encoding nucleic acid determines the corresponding encoded protein's structural and functional properties. Predictability of which changes can be tolerated in an encoded protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which the

proteins' structure relates to its function. The positions within an encoding nucleic acid's sequence where modifications can be made with a reasonable expectation of success in obtaining an encoded polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. In this case, the necessary guidance has not been provided in the specification as explained in detail above. Thus, a skilled artisan would recognize the high degree of unpredictability that the entire scope of polynucleotides would encode a polypeptide having the desired activity. Regarding claims 30 and 33, it is noted that, without the necessary guidance, the ability to use a nucleic acid as a therapeutic agent is highly unpredictable.

- The state of the prior art supports the high degree of unpredictability: Regarding claims 7, 10, 81, and 83-84, the state of the art provides evidence for the high degree of unpredictability in altering a polynucleotide sequence with an expectation that the encoded polypeptide will maintain the desired activity/utility. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991) teach "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). While it is acknowledged that this reference was published in 1991, to date there remains no

certain method for reasonably predicting the effects of even a *single* amino acid mutation on a protein. Such mutations may even completely alter a protein's activity. As a representative example, Witkowski et al. (*Biochemistry* 38:11643-11650) teaches that a single amino acid substitution results in conversion of the parent polypeptide's activity from a beta-ketoacyl synthase to a malonyl decarboxylase (see e.g., Table 1, page 11647). Thus, the prior art acknowledges the unpredictability of altering a protein-encoding sequence with an expectation of obtaining a protein having a desired function and discloses that even a single substitution in a polypeptide's amino acid sequence may completely alter the function of a polypeptide. Regarding claims 30 and 33, without the necessary guidance it is highly unpredictable as to what diseases can be effectively treated using a "pharmaceutical composition" comprising a NOVX8-encoding polynucleotide, particularly those employing polynucleotide-based treatments. As the specification lacks the necessary guidance for preparing and using a "pharmaceutical composition" comprising a NOVX8-encoding polynucleotide for achieving a therapeutic effect, one of skill in the art would recognize the high degree of unpredictability for making and using the claimed/recited "pharmaceutical composition". For example, Dang et al. (*Clin Can Res* 5:471-474), in a report summarizing the status of gene therapy disclose, "The obstacles surrounding effective human gene therapy have been studied by the Orkin-Motulsky Committee commissioned by Dr. Harold Varmus, director of the NIH (Bethesda, MD). This committee found human gene therapy to be an immature science with limited understanding of gene regulation and disease models for pre-clinical studies" (page 471, left column, middle). Furthermore, Fox (*Nat Biotechnol*

21:217), citing a finding that gene therapy for treatment of X-SCID has been correlated with incidence of leukemia, suggests that even gene therapy that successfully achieves a therapeutic effect may have unpredictable deleterious side effects. Thus, based on the state of the art, a skilled artisan would recognize the high degree of unpredictability in using a "pharmaceutical composition" comprising a NOVX8-encoding polynucleotide for achieving a therapeutic effect.

- The amount of experimentation required is undue: While methods of generating variants and isolating homologues of a given polynucleotide are known in the art, e.g., mutagenesis and hybridization, it is not routine in the art to screen for *all* polynucleotides having a substantial number of substitutions or modifications and encoding polypeptides having *any* function, as encompassed by the instant claims. Furthermore, it is not routine in the art to determine the formulation, dosage, and route of administration for using a nucleic acid for a therapeutic effect – if any.

Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation that is required, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired

biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

[17] It is noted that the instant application claims domestic priority to numerous provisional applications. For purposes of establishing the priority date of the instant application, the examiner requests that applicants indicate, in the response to this Office action, the provisional application(s) that provide(s) support for the claimed invention.

[18] Claim 7 is rejected under 35 U.S.C. 102(e) as being anticipated by Burgess et al. (US Patent Application Publication 2002/0137202). Claim 7 is drawn to an isolated nucleic acid encoding a polypeptide comprising the amino acid sequence of a naturally-occurring polypeptide variant of SEQ ID NO:24. The reference of Burgess et al. teaches

a nucleic acid (SEQ ID NO:21 of Burgess et al.) that encodes a naturally occurring variant of SEQ ID NO:24 (See Appendix A). This anticipates claim 7 as written.

[19] Claim 10 is rejected under 35 U.S.C. 102(b) as being anticipated by GENBANK accession number AI739096 (GI:5101077). Claim 10 is drawn to an isolated nucleic acid molecule that hybridizes under stringent conditions to SEQ ID NO:23 or a complement thereof. GENBANK accession number AI739096 teaches a nucleic acid that is 100% identical to nucleotides 89-456 of SEQ ID NO:23 (see Appendix B) and thus, would hybridize under stringent conditions to the complement of SEQ ID NO:23. This anticipates claim 10 as written.

Conclusion

[20] Status of the claims:

- Claims 5-10, 12-14, 30, 33, and 78-84 are pending.
- Claims 5-10, 12-14, 30, 33, and 78-84 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 7:00 am to 3:30 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (703) 872-9306. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

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